

Letter to the Editor

Down Syndrome and Natural Family Planning

To the Editor:

Castilla et al. [1995] report that users of natural family planning (NFP) produced no excess of Down syndrome (DS) infants. The finding is relevant to the question of whether DS is sometimes the consequence of the fertilization of an oocyte which is "overripe." That question achieved prominence in the hypothesis of German [1968] that the decline in coital rate with maternal age results in a rise in the proportion of such late fertilizations, thus accounting for the maternal age effect in DS. It was shown mathematically that this decline could not alone be responsible for the magnitude of this maternal age effect [James, 1968].

However, this does not totally dispose of the hypothesis that overripe oocytes are involved in the production of DS conceptuses. To test this in users of natural family planning (NFP), we need to identify those who were actually observing the method in the conception cycle viz. the method failures. Castilla et al. [1995] give no indication that they have restricted their sample in this way. If they did not so restrict their sample, this must weaken their conclusion that there is no association between DS and NFP.

The point is worth pursuing, because the overripe oocyte hypothesis has an attractive aspect in regard to DS that I have not previously seen mentioned. There is an excess of males among DS children [Bernheim et al., 1979; Nevin et al., 1982; Nielsen et al., 1981]. This *may* be due to sex-selective spontaneous abortion [Boué and Boué, 1973; Huether et al., 1992]. However, there is another possible cause. There is now strong evidence that inseminations early and late in the cycle are more likely than others to lead to male conceptions [Guerrero, 1974; Harlap, 1979; Gray, 1991]. Similar phenomena have been reported in a number of other mammalian species [for references, see James, 1994]. Of particular relevance in this context, and partially underlying the above conclusion, are the reports of a male excess in NFP failures [France et al., 1984; Gray and Kambic, 1988; WHO Task Force, 1984; Shiono et al., 1982; Perez et al., 1985]. Hence, if the "overripe oocyte" hypothesis were correct in regard to DS, the curious sex ratio of DS cases would be expected, rather than requiring the invocation of sex-selective spontaneous abortion of DS fetuses, for which the present evidence seems equivocal.

Lastly, it has been reported that even when maternal age is controlled, higher rates of DS births occur to Catholic women [Sigler et al., 1967; Mulcahy, 1978]. This invites further suspicion concerning the implication of NFP.

REFERENCES

- Bernheim A, Chastang C, de Heaulme M, de Grouchy J (1979): Excess of males in Trisomy 21. *Ann Génét (Paris)* 22:112-114.
- Boué J, Boué A (1973): Les avortements spontanés humains. *Études cytogénétiques et épidémiologiques. Rev Fr Gynécol* 68:625-643.
- Castilla EE, Simpson JL, Queenan JT (1995): Down syndrome is not increased in offspring of natural family planning users: Case-control analysis. *Am J Med Genet* 59:525.
- France JT, Graham FM, Gosling L, Hair PI (1984): A prospective study of the preselection of the sex of offspring by timing intercourse relative to ovulation. *Fertil Steril* 41:894-900.
- German J (1968): Mongolism, delayed fertilization and sexual behaviour. *Nature* 217:516-518.
- Gray RH (1991): Natural family planning and sex selection: Fact or fiction? *Am J Obstet Gynecol* 165:1982-1984.
- Gray RH, Kambic RT (1988): Epidemiological studies of natural family planning. *Hum Reprod* 3:693-698.
- Guerrero R (1974): Association of the type and time of insemination within the menstrual cycle with the human sex ratio at birth. *N Engl J Med* 291:1056-1059.
- Harlap S (1979): Gender of infants conceived on different days of the menstrual cycle. *N Engl J Med* 300:1445-1448.
- Huether CA, D'Souza SD, May KM, Kelly JC, Baird PA (1992): Fetal and live birth sex ratios in autosomal aneuploids. *Am J Hum Genet [Suppl]* 51:339 (abstract).
- James WH (1968): Mongolism, delayed fertilization and sexual behaviour. *Nature* 219:279-280.
- James WH (1994): Cycle day of insemination, sex ratio of offspring and duration of gestation. *Ann Hum Biol* 21:263-266.
- Mulcahy MT (1978): Down syndrome and parental coital rate. *Lancet* ii:895.
- Nevin NC, Little J, Coffey W (1982): Down syndrome in Northern Ireland. *J Med Genet* 19:459.
- Nielsen J, Jacobsen P, Mikkelsen M, Niebuhr E, Sorensen K (1981): Sex ratio in Down syndrome. *Ann Génét (Paris)* 24:212-215.
- Perez A, Eger R, Domenichini V, Kambic R, Gray RH (1985): Sex ratio associated with natural family planning. *Fertil Steril* 43:152-153.
- Shiono PH, Harlap S, Ramcharan S (1982): Sex of offspring of women using oral contraceptives, rhythm, and other methods of birth control around the time of conception. *Fertil Steril* 37:367-372.
- Sigler AT, Cohen BH, Lilienfeld AM, Westlake JE, Hetzenecker WH (1967): Reproductive and marital experience of parents of children with Down's syndrome (mongolism). *J Pediatr* 70:608-614.
- WHO Task Force (1984): A prospective multicentre study of the ovulation method of natural family planning. IV. The outcome of pregnancy. *Fertil Steril* 41:593-598.

William H. James
The Galton Laboratory
University College London
London, UK

Received for publication December 28, 1995; revision received April 26, 1996.

Address reprint requests to William H. James, The Galton Laboratory, University College London, Wolfson House, 4 Stephenson Way, London NW1 2HE, UK.